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able to interact in-situ with at least the $\alpha 7$ subunit of such
proteasomes as are present within the cytoplasm of the cell; and
able to alter the functional proteolytic activity of said proteasomes
having an interacting $\alpha 7$ subunit such that a markedly increased
expression of at least one specific peptide occurs in-situ.

REMARKS

The Examiner has objected to the Specification regarding the content of original pages 12, 19, and 27 respectively. In addition, the Examiner has rejected the original claims under 35 U.S.C. 112, first paragraph as containing subject matter which was not described within the Specification sufficiently; and rejected the claims under 35 U.S.C. 112, second paragraph as being indefinite in language for specifically stated reasons. Finally, the Examiner has rejected the claims under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over U.S.P.N. 5, 654, 273. In response, applicants have amended the Specification; added new Figs. 8-10 respectively; amended original claims 1-2, 5-6, 9-10, and 11-14; added new independent claim 15; and enclose herewith several publications addressing the pertinent technical

field. By these amendments and enclosures, applicants believe they have overcome and obviated each basis for objection and rejection stated by the Examiner in the instant first Official Action.

As a preliminary matter, applicants address the objection to the Specification made by the Examiner regarding the content of original pages 12, 19, and 27. While the grounds for such objection are unstated as well as questionable, applicants nevertheless have acquiesced to the Examiner's position and deleted the content of original pages 12, 19, and 27 respectively. In addition, applicants have amended the Specification text at page 7, line 19 to present new figure descriptions briefly for newly added Figs. 8, 9, and 10 respectively which present again the entire content of Flow Scheme A, Table 3, and Table 4 as such. Applicants respectfully question the Examiner's need for such strict formality as well as the Examiner's standard for evaluating and deciding what constitutes proper subject matter for inclusion as a table rather than what must be presented in the drawing as such. Nevertheless, applicants have added new Figs. 8, 9, and 10 respectively and acceded to the Examiner's explicit demands on this issue. For these reasons, applicants therefore request that the Examiner reconsider her

stated position and withdraw this ground of objection against the Specification.

Applicants will now address each substantive basis for rejection stated by the Examiner in the instant Official Action with respect to both the legal requirements and the relevant factual circumstances. Because so much of the Examiner's stated views and positions are dependent upon a clear reading and understanding of applicants' definition as defined by the now pending claims, applicants deem it both useful and necessary to summarily review the subject matter as a whole which is applicants' claimed invention.

I. Applicants' Invention as Claimed.

Applicants' invention is defined in the alternative by amended claims 1-10 and by claims 11-15. Claims 1-10 define a method while claims 11-15 are composition of matter definitions directed to new biologically active compounds intended for use in the methodology.

It will be recognized and appreciated that amended independent claim 1 is directed to a method for stimulating angiogenesis within a targeted collection of viable cells in-situ;

whereas amended independent claim 2 defines a method for a discriminating inhibition of proteasome-mediated degradation of peptides in-situ within a collection of viable cells. These amended independent method claims are images of one another in their requirements and in the results produced. Each of these method claims identifies a collection of cells in-situ as the target; provides means for introducing at least one member selected from the group consisting of the PR-39 oligopeptide collective to the cytoplasm of the targeted cells; introduces at least one member of the PR-39 oligopeptide collective to the targeted cells; and then explicitly requires that the introduced PR-39 oligopeptide collective member interact with such proteasomes as are present within the cytoplasm of the targeted cells such that at least three specifically stated events must occur. These are: at least the $\alpha 7$ subunit of the proteasomes interacts with the introduced PR-39 oligopeptide collective member; at least a part of the proteolytic activity mediated by these proteasomes having an interacting $\alpha 7$ subunit becomes functionally altered; and the functionally altered proteolytic activity of these proteasomes results in a stimulation of angiogenesis in-situ or results in a discriminating inhibition of

proteasome-mediated degradation for at least one specific peptide (such as IKB α or HIF-1 α).

It will be appreciated also that applicants' invention as defined by amended claims 1-10 individually is presented in the form of a method or process having a series of explicitly stated manipulative steps. As codified in 35 U.S.C. 100(b), method claims may include a new use of a known process, machine, manufacture, composition of matter or material; and this form of claiming also applies to a newly recognized use for a composition of matter regardless of whether the material is a previously known composition or an entirely novel composition. Accordingly, the essential question for the Examiner for purposes of 35 U.S.C. 102 and 103 is -- whether the claimed method of use is novel and non-obvious to a person of ordinary skill in the field of the invention. Equally important, when evaluating the novelty and patentability of applicants' defined method claims, it is not pertinent whether the compositions of matter themselves are known, or are new, or are themselves unobvious. The true issue is exclusively whether the utility defined by the method claims would have been known or obvious in light of the teachings in the prior art references given the perspective of the ordinary practitioner in that field [In re May, 197 U.S.P.Q. 601 (C.C.P.A. 1978)].

Also it will be recognized that each of the dependent claims 3-10 respectively depend from at least one of amended independent claims 1 or 2 individually. Accordingly, the subject matter as a whole is now most broadly defined by amended independent claims 1-2 individually and collectively. Applicants therefore request that the Examiner carefully consider the marked differences in definition and substance presented by amended independent claims 1 and 2 now pending in the present application.

Finally, pending claims 11-15 are composition of matter claims which define a family of PR-39 derived oligopeptides whose members are biochemically active and individually cause a functional inhibition of proteasome-mediated degradation for at least one specific peptide in-situ after being introduced to a viable cell. Amended independent claim 11 specifies five specific requirements for each member in this family of oligopeptides. These requirements include the maximum length of the oligopeptides which is substantially less than 39 amino acid residues in length; is at least partially homologous with the N-terminal amino acid sequence of the native PR-39 peptide; begins with the sequence Arg-Arg-Arg at the N-terminal end; is able to interact in-situ as part of its biochemical activity with at least $\alpha 7$ subunit of such proteasomes as are

present within the cytoplasm of the cell; and are able to alter the functional proteolytic activity of these proteasomes such that a marked increase expression of at least one specific peptide occurs as a consequence. Newly added independent claim 15 mirrors the requirements of amended independent claim 11, except that the requisite peptide length must be less than 20 amino acid residues.

In addition, the Examiner will recognize that, not only do the members of this oligopeptide family each have and demonstrate these specific interaction requirements, but also that these members are individually biologically active to cause a functional inhibition of proteasome-mediated degradation in-situ. Three of the preferred compositions constituting members of this oligopeptide family are defined as specific amino acid residue sequences by dependent claims 12, 13, and 14 respectively. It will be noted and appreciated that these dependent claims define members having 15, 11, and 8 amino acid residues; and in that the individual amino acid sequence for each of these residue lengths is specifically stated as beginning at the N-terminal end with the sequence Arg-Arg-Arg.

II. The Rejection of Claims under 35 U.S.C. 112, First Paragraph.

The Examiner has rejected original claims 1-10 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the Specification sufficient to meet the "written description" requirement as such. It is necessary, therefore, to have a proper understanding and appreciation of what is needed in order to satisfy the "written description" legal requirement.

A fairly uniform standard presently exists for determining if the written description requirement of 35 U.S.C. 112, first paragraph has been sufficiently complied with and satisfied by the disclosure of a Specification in a pending application. The case law decisions and legal analyses to date state that the test for legal sufficiency of descriptive support in Specification's disclosure is: whether or not the disclosure of the pending application reasonably conveys to the person of ordinary skill in that art that the inventor had possession of the innovative subject matter as then defined by the pending claims. Thus, to be legally sufficient, the written description must clearly allow persons of ordinary skill in the art to recognize that, after reading the Specification text, applicant invented that which is claimed [In re Gosteli, 10 U.S.P.Q.2d 1614 (Fed. Cir. 1989); In re Kaslow, 217 U.S.P.Q. 1089 (Fed. Cir. 1983)].

For this inquiry, fact specificity is central and essential to deciding the issue. When evaluating and deciding the adequacy of written description, the primary consideration in each instance for the Examiner is the quality and quantity of factual detail provided by the disclosure - which in turn, must and will depend upon and vary with the nature of the subject matter which is the invention as well as determine the amount or degree of information and knowledge properly needed to be imparted to those of ordinary skill in the art by the Specification text [In re Wertheim, 169 U.S.P.Q. 795 (CCPA 1971); Vas-Cath Inc. v. Makurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991) and the citations listed therein at p. 1116].

These case law decisions routinely point out and stress that the written description requirement of Section 112 is an issue which must be decided on its own facts in each instance with due regard for the nature of the specific invention, the scope of the claims as written and the state of then existing pertinent knowledge in that art or technical field. Overall therefore, legal compliance requires merely that the written description when reviewed in its entirety provide and place in the reader that knowledge and information constituting what applicant considers and claims as his own invention in such degree that the invention as disclosed and claimed can be understood in full and clearly distinguished from that which is already known or in common use [In re Smith and Hubin, 178

U.S.P.Q. 620 (CCPA 1973); In re Wright, 9 U.S.P.Q.2d 1649 (Fed. Cir. 1989); Ralston Purina Co. v. Far-Mar-Co. Inc. 227 U.S.P.Q. 177 (Fed. Cir. 1985); Vas-Cath Inc. v. Makurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991)].

Applicants now direct the Examiner's attention to Specification text in order to demonstrate the presence of an ample and complete description for each and every component part of the methodology broadly defined by amended independent claims 1 and 2 respectively herein. The underline mechanism for the method is described beginning at page 9, line 19, and continues through page 11, line 1. As repeatedly disclosed therein, the essential requirement is the presence of a proteasome and at least one member of the collective of PR-39 oligopeptides. The detailed description of proteasomes, their activity and polypeptide degradation function is described in abundant and extraordinary detail at pages 11 through 21, in which the structure - including $\alpha 7$ subunit as such - is identified in detail. The common knowledge regarding the $\alpha 7$ subunit, its nomenclature and its physical properties, is described by a variety of conventionally known information and facts cited as such within Tables 2 and 3; and the overlapping nomenclature and terminology which identifies HsC8 and $\alpha 7$ as the same subunit is given explicitly. In addition, applicants hereby enclose a copy of the explicitly cited publications in Tables 2 and 3 (as well as several

others) which further describe in detail the common knowledge conventionally shared in this art.

In addition, the membership of the PR-39 oligopeptide collective is also described in precise, clear, and explicitly complete detail within the Specification beginning at page 22, line 6 and continuing through page 29, line 8. In addition, the means for introduction of the specific member peptide, especially the shorter length derived homologues, are described in depth beginning at page 29, line 13 and continuing through page 35.

The Examiner has specifically focused her remarks [as stated at page 2, bottom and page 3, top of the instant Official Action] on the word "selectively" and the use of this word within the specific manipulative steps recited by amended independent claims 1 and 2 explicitly. Accordingly, it should be recognized from the description and disclosure provided by the Specification text itself that the term "selective alteration" refers to the fact that upon binding to any member of the PR-39 oligopeptide collective, the $\alpha 7$ subunit of the proteasome becomes functionally altered in such a way as to inhibit degradation of specific peptides such as HIF-1 α and IKB α - but without interfering with or otherwise disrupting the overall proteolytic proteasome function. Thus, the definition of "selectivity" is functional as disclosed and described by the

Specification and as defined by the precise language of amended independent claims 1 and 2 herein.

This functional alteration of polypeptide degradation by the $\alpha 7$ subunit is demonstrated and evidenced in particular by the experiments and empirical data presented by the Specification text beginning at page 36 and continuing through page 46. Attention is directed in particular to the following experiments: Experiment 1 described at page 39-40 empirically shows the interaction of PR-39 peptide and the $\alpha 7$ subunit of proteasomes. Attention is directed in particular to page 39, line 18 through page 40, line 18 and Figs. 1A-1D inclusive. This experiment and data reveal that PR-39 peptide interacts with the $\alpha 7$ subunit of proteasomes as specified by amended independent claims 1 and 2 explicitly.

Experiment 2 described at page 40, line 21 and continuing through page 42, line 10 of the Specification demonstrates the ability of the PR-39 peptide members to affect proteasome function in-vivo, via the functional change for IKB α processing. The results are illustrated by Figs. 2A-2D respectfully which show that the PR-39 peptide mediated the inhibition of degradation in the cells under test.

In additon, Experiment 5 shows the stimulation of angiogenesis directly in cells and tissues via the introduction of the PR-39 peptide in a

mice matrigel assay system. The experiment is described within the Specification beginning at page 44, line 11 and continues in detail through line 23. The results of the empirical evaluations show direct evidence for angiogenesis as a consequence of introducing the PR-39 peptide.

Particular attention is also directed to Experiment 6 which utilizes a 11 amino acid residue peptide as the specific composition under test in a mouse matrigel assay system. As evidenced by the experiment described at page 45, lines 1-24 and Fig. 7, use of the short length PR-11 peptide resulted in marked angiogenesis under the experimental conditions described; and demonstrates the biological activity of and legal utility for shorter length peptides which collectively are all members of the PR-39 derived oligopeptide family. This experiment is factual evidence and proof that these shorter-length peptides are both biologically active as such and effective in stimulating angiogenesis in-vivo.

Finally, applicants direct the Examiner's attention to the stated conclusions presented at page 46 of the Specification text. The first full paragraph specifically identifies the effect of direct interaction between the $\alpha 7$ subunit with the different peptides constituting the PR-39 oligopeptide collective as described and defined previously within the Specification text. Equally important, the second full paragraph

appearing at lines 11-21 of page 46 identify and review in summary form what are the demonstrated effects and results of using such polypeptides.

Thus, with respect to the Examiner's explicitly stated views and positions on this issue, applicants respectfully submit and affirm that there is no information or descriptive content which has been omitted or is otherwise missing from the written disclosure of the Specification text which could meaningfully effect or influence the knowledge and understanding of the ordinary practitioner skilled in this art. The Examiner has questioned and rejected the original claims primarily on the basis of the term "selectively". Applicants have deleted this term entirely from the language of amended independent claims 1 and 2. Instead, the presently pending claim language identifies the functional alteration and changes with greater precision and specificity. The functional alteration specificity includes what is the $\alpha 7$ subunit of the proteasomes and how these are functionally altered; the means of introduction; and the way the degradation process and proteolytic activity of the proteasomes has been functionally altered and markedly changed when a member of the PR-39 oligopeptide collective interacts with the $\alpha 7$ subunit of the proteasomes then present within the cytoplasm of the targeted cells.

Applicants respectfully submit that all the detailed information and knowledge presented by the Specification text, and especially the

experiments and empirical data presented, illustrate, demonstrate, and unequivocally provide more than ample and adequate detailed knowledge and information that the invention defined by the amended independent claims 1 and 2 is the very subject matter as a whole invented by applicants. In short, applicants respectfully submit that the Examiner has no factual basis on which to question the adequacy or sufficiency of the "written description" as presented by this Specification text.

The Examiner has also questioned the utility of the composition claims defined by original claims 11-14. The description of utility and empirical data demonstrating and exemplifying such utility is presented in detail within the Specification text as demonstrated by the discussion presented herein. Not only is the mechanism of interaction described in detail along with the intended results of consequences of such explicit interaction; but also empirical data showing the biological activity and functional efficacy of shorter length peptides has been demonstrated directly by Experiment 6 described at page 45 of the Specification text. Applicants respectfully submit that the detailed description of the Specification generally as well as the specifics of Experiment 6 appearing at page 45 of the Specification text contradict and deny the view and position explicitly stated by the Examiner at page 3, last paragraph of the

instant Official Action. The Examiner has demanded direct evidence of utility; and applicants have shown that such direct evidence presently exists and is described and disclosed by the Specification text itself. Thus, the factual basis which the Examiner must have in order to put forward a prima facie rejection based on a failure of utility is directly contradicted and nullified by the very written description and experimental evidence provided by applicants' Specification.

Applicants have gone to considerable length in order to demonstrate the factual adequacy and legal sufficiency of the methodology disclosed by the Specification and defined by amended independent claims 1 and 2 respectively. The Specification text provides more than ample descriptive content, details, examples, and experiments and empirical data to show applicants have full and complete possession of the invention defined by amended independent claims 1 and 2. The disclosure of the Specification text presents a quantum and quality of detailed information and knowledge that any person of ordinary skill in the art will and must recognize that, after reading the disclosure of the Specification, applicants invented precisely that which is claimed. For all these reasons, applicants therefore respectfully request that the Examiner reconsider her stated position and withdraw this ground of rejection against all the presently pending claims.

III. The Rejection of the Claims Under 35 U.S.C. 112, Second Paragraph.

The Examiner has rejected original claims 1-10 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention. The problem again appears to be focused and centered on the use of the word "selectively" and the manner in which the term "selectively inhibited" is employed within the claim language.

The Examiner has stated a reluctance and personal opposition to the word "selectively" as employed within the language of the original claims defining the methodology. As shown repeatedly and described explicitly by the Specification text, the selective alteration of the $\alpha 7$ subunit of proteasomes has been described, explained, and shown experimentally. The selective nature of this alteration refers clearly to the evidence and fact that when a member of the PR-39 oligopeptide collective is added to a targeted cell, there is interaction with the $\alpha 7$ subunit; and this subunit becomes altered functionally such that the

degradation of specific peptides such as HIF-1 α and IKB α is inhibited without interfering with the other proteasome functions overall. Thus as employed within the original claim language, the meaning of the term "selectively" is and remains a functional change.

In order to resolve such questions, applicants have amended the language of the methods defined by independent claims 1 and 2; and deleted the term "selectively" and substituted instead the word - - functionally - -. In this manner, the essence of the Examiner's stated view and position has been effectively met and satisfied; yet, the true meaning and precise recitation of manipulative steps with the intended result remains explicitly set forth with particularity and precision.

Similarly, the specific wording of dependent claims 9 and 10 respectively have been amended to delete the term "selectively" and insert the word - - markedly - -. Such amendment is believed to be not only proper, but also focuses on and emphasizes the degree in which the selective alteration is changed or inhibited.

Overall therefore, applicants have substantively amended claims 1-2, 5-6, 9-10 and 11-14 individually. Each of the flaws in wording identified by the Examiner have been addressed in these claims; and the language has been amended to define better and more precisely the particular points the subject matter as a whole which is applicants' invention. The

amended language of all these claims is now believed to be correct, precise, and satisfactory in all respects with regard to the requirements of the second paragraph of 35 U.S.C. 112.

In addition, as regards the language of the pending claims as a whole, the first inquiry is to determine whether the claims do, in fact, set out and circumscribe a particular area or subject matter with a reasonable degree of precision and particularity. It is here where the meaning of the language employed to define the invention is analyzed; not in a vacuum, but always with regard to the teachings of the prior art and within the particular use or application disclosed by the Specification as it is understood and interpreted by one possessing ordinary skill in the pertinent art [In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976)]. Applicants note that each of the terms used in claims 1-15 are well understood; are not subject to numerous definitions and interpretations; and that with regard to the antecedent description of the Specification text, there is no discrepancy, no confusion, and no ambiguity. Rather, the claims as a whole now pending read on subject matter which is completely disclosed and enabling within the Specification text; moreover, each of the pending claims is explicit and clear, and sets out and circumscribes the particular subject matter area with the requisite reasonable degree of precision and particularity [In re Moore, 169 U.S.P.Q. 236 (C.C.P.A. 1971)].

For these reasons, applicants respectfully submit that each and every claim now pending satisfies the requirements of precision, clarity, and particularly required by the second paragraph of 35 U.S.C. 112. Accordingly, applicants respectfully request that the Examiner reconsider her stated position and withdraw this ground of rejection against the presently pending claims.

IV. The Rejections Under 35 U.S.C. 102(b) and 103(a).

The Examiner has rejected original claims 1-10 under 35 U.S.C. 102(b) as anticipated by, or in the alternative, under 35 U.S.C. 103(a) as being obvious over the Gallo et al. reference, U.S. Patent No. 5, 654, 273. The rationale of the Examiner explicitly states that the '273 patent reference discloses a method for treating angiogenesis by using PR-39 and that this patent reference constitutes relevant prior art. However, because the claims in the present application are drawn to a method of using a known peptide for treating a condition taught by the art - regardless of the mechanism of action - applicants' pending claims have been deemed to be "inherently anticipated and/or rendered obvious by the art."

Applicants respectfully point out and affirm that the Examiner is factually incorrect and legally in error as regard to the issues of novelty and non-obviousness. The Examiner has noted explicitly at page 3, last full paragraph that cited and applied Gallo et al. patent reference requires that the necessary number of amino acid residues in the peptide sequence (and any of its modified forms) require the presence of all 39 amino acid residues for the peptide to show biochemical activity. The Examiner has herself pointed purposely to column 3, lines 26 + as evidence of this fact.

Moreover, the Examiner has openly acknowledged and recognized that the single cited and applied reference (the '273 patent), does not explicitly or directly teach or disclose those particular attributes, properties and capabilities of the method defined by the previously pending claims 1-10. Instead, the entirety of the Examiner's reasoning is based on inherency; and the Examiner's remarks and conclusions rely upon the view that the individual peptides described in the '273 patent inherently possesses the characteristics recited in the instant claims and therefore anticipate the method comprising applicants' invention - - or therefore make the method of the invention an expected and predictable modification of what is actually disclosed by the patent reference. The entire substance of the Examiner's presentation, rationale, and position is

thus centered on the legal doctrine of inherency as it applies to this single prior art reference. Accordingly, a summary review and proper understanding of the legal doctrine of "inherency" is necessary.

The legal doctrine of "inherency" holds that anticipation (and also in this instance obviousness) may be established when one (or a combination of prior art references) either discloses exactly or suggests overtly a claimed invention; and also is established when the natural and invariable practice of the references' disclosure would necessarily and reasonably intrinsically meet all the elements of the invention as presently claimed.

Unfortunately, the Examiner has failed to recall that the legal doctrine of inherency is available only when the claimed invention can be identified or inferred from the disclosure within the prior art reference with substantial certainty. Probabilities and speculation are not a substitute for substantial certainty; and probabilities and speculation are not legally sufficient to invoke and apply the inherency doctrine [In re Oelrich, 212 U.S.P.Q. 323 (C.C.P.A. 1981); In re Chandler, 117 U.S.P.Q. 361 (C.C.P.A. 1985)].

In order for a claimed invention to be inherently disclosed, the defined invention claimed in the pending patent application must be the necessary and only reasonable construction to be given to the prior art

disclosures; and the resultant claim must inevitably occur and be the result of what is revealed in the prior art. Moreover, the mere fact that a certain thing may or might possibly result from the set of factual circumstances is not legally sufficient to establish inherency [In re Robertson, 49 U.S.P.Q.2d 1949 (Fed. Cir. 1999)]. The legal burden thus lies upon the Examiner to demonstrate that any of the cited and applied prior art references provide the desired result, consequence, property, or trait with substantial certainty. If, however, the consequence, property, or result could only potentially or speculatively occur as a theoretical possibility or contingent event within the factual setting, then this basis is inadequate legally and insufficient [Continental Con Co. U.S.A. Inc. v. Monsanto Co., 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991)].

It is therefore well established, as a matter of law, that for an attribute or result to be deemed as inherently disclosed or suggested, it is not sufficient that the ordinary person following the prior art disclosure(s) might obtain the result set forth. To the contrary, it is legally demanded that the attribute or result must invariably happen. Inherency as a doctrine and legal basis cannot be established upon a speculation or where reasonable doubt as to the occurrence of the inevitable result exists [In re Wertheim, 191 U.S.P.Q. 90 (C.C.P.A. 1976)].

The factual basis which the Examiner implies as underlining support for inherency rejection must be read and understood as written. Attention is thus directed to column 3, lines 26-45 in particular as the essence of what the Examiner has employed wrongly ; and subjectively as the factual basis. This detailed disclosure identifies and specifies the following points of information: (1) The PR-39 amino acid sequence must be employed at a minimum as a 39 amino acid residue sequence in order for biological activity to be demonstrated. (2) The entire 39 amino acid sequence of PR-39 can be part of a larger sized molecule such as a fusion protein, or when a mobilized to an inert substrate or targeted using a specific ligand, as part of a longer length protein. (3) The entire PR-39 peptide and any of its longer length products are collectively identified as "synducin" - which are all characterized by a specific biological activity as described in the examples within columns 6-10 respectively. (4) The "synducin" characteristics and by specific biological activity are shown by specific inducement of syndecan-1 and syndecan-4 expression on the surface of mesenchymal cells, or by specific inducement of syndecan-1 and syndecan-4 mRNA within cells, or by an increase in the level of cell surface heparan sulfate and rapid up take of such heparan sulfate into mesenchymal cells to a saturation level. (5) The biochemically active PR-39 compositions must include a specific and lengthy amino acid

sequence which is: PRO - PRO - X - X - PRO - PRO - X - X - PRO and PRO - PRO - X - X - X - PRO - PRO - X - X - PRO, where X is any amino acid.

These are explicit, direct, and unrelenting requirements for the peptide compositions and the limited biological activities specified as the utility and function for these compounds. There is no information and no suggestion whatsoever for the use of these peptides collectively other than the specific inducement of syndecan-1 and syndecan-4 expression on the surface of mesencymal cells. The entire mechanism and methodology of synducin effects regardless of intended use is specified and compulsory by the very limits of description and outcome requirement as specified within column 3, lines 25-46.

Moreover, the entire mechanism and methodology of use for any and all purposes is stated explicitly at column 5, lines 1-60; this disclosure demands that the inducement of syndecans on the cell surface be part of each and every usage clinically or otherwise. Thus, any methodology which employs and relies on the information disclosed by this '273 patent reference must incorporate all these limitations and restrictions as stated explicitly in order for any utility or clinical result to be expected or foreseen.

Equally important, the selectivity of the method and compositions is explicitly restricted as demonstrated within Example 4 disclosed at column

8, lines 51-65. It is noted that the use of these peptides failed to perform or be effective in a variety of non-mesenchymal cells as tested; and showed that if the cells were not mesenchymal cells as such, no response or biochemical activities was demonstrated or could be expected [Column 8, lines 60-65].

In addition, applicants have recently found another publication which further demonstrates and reinforces the limited nature of expectations for the PR-39 peptide as a biochemically active composition. This publication is U.S. Patent No. 5, 830, 933. A copy of the issued patent is enclosed for the Examiner's information and review.

In sum, all the information disclosed or suggested by the Gallo et al. patent reference is self-limiting, self-contained and extraordinarily restrictive in its requirements and characteristic uses. Applicants therefore respectfully submit and affirm that the Examiner's position and presumption as stated is a fallacy and the Examiner's reliance upon inherency is based solely upon an unproven and speculative theory which has no factual basis to support it. Applicants also respectfully maintain that the Examiner has not presented or established any evidence with the requisite degree of substantial certainty which proves any inherent property with regard to angiogenesis capabilities or the discriminating inhibitory properties of the methods now recited by amended

independent claims 1-10 herein. The Examiner's reliance and use of the inherency doctrine fails blatantly and may not be properly employed as a legal basis for rejection because the entirety of the rationale in evidence employed by the Examiner as the underline basis for rejection is purely speculative and can at best be identified and characterized as a theory without any realistic probability as such. This is evidenced and demonstrated factually by the complete absence of relevant information, knowledge, or data in the cited and applied '273 patent - which is devoid of any direct or explicit mention of proteasomes, the $\alpha 7$ subunit, and any functional changes in peptide degradation properties.

The Examiner has not utilized this '273 patent reference with regard to the composition claims recited by pending claims 11-15 herein. Applicants note that this prior art reference teaches away from the very characteristics, properties, and utilities demonstrated by applicants' defined invention. Applicants note in particular that the short length peptide constituting the compositions defined by claims 11-15 are all far shorter in length than the minimum 39 amino acid residues in length; are not part of a fusion peptide or linked with any other molecule; and do not comprise or contain the requisite amino acid sequences involving the PRO sequences and linkages which are explicitly required by the disclosure stated at column 3, lines 30-35 of the reference. Moreover, the

Examiner has explicitly recognized that the Gallo et al. reference requires the presence of all 39 amino acids at a minimum in order for any biological activity to be demonstrated for any purpose whatsoever. Thus, the Examiner has no basis at all for suggesting, inferring, or believing that any shorter length peptide sequence - particularly those lengths of 15, or 11, or 8 residues - could or would be biologically active or useful for any purpose at all.

Applicants also therefore affirm and maintain that the prior art reference of record does not teach and could not suggest to those of ordinary skill in the art that they should carry out the claimed process defined by independent claims 1-10 or employ the compositions defined by claim 11-15. Moreover, the single reference of record has also revealed that, even if the ordinary practitioner had thought of making or practicing applicants' claimed invention, those of ordinary skill in this field would not have a reasonable expectation of success. Applicants further maintain and submit that there is nothing inherent or intrinsic in the totality of the cited and applied prior art of record in combination which provides a basis for any expectation which would render the subject matter of independent claims 1-15 respectively as being either implied or obvious. Accordingly the subject matter as a whole defined by independent

claims 1-15 recite a methodology and compositions which are non-obvious and have substantial patentable merit.

Applicant respectfully submits also that the Examiner unfortunately has also made a number of different, major prejudicial errors of law regarding the patentability of the presently pending claims with regard to Section 103(a). These include the following kinds of errors: the Examiner has failed to establish a prima facie case of anticipation or of obviousness which is the Examiner's exclusive legal burden [In re Piasecki, 223 U.S.P.Q. 785 (Fed. Cir. 1984)]. Applicants respectfully submit that the publication of record fails to provide sufficient factual support or evidence, direct or inherently, that the presently claimed subject matter is known, or suggested, or inferable to any person of ordinary skill in this art. As applicants have demonstrated herein, the state of knowledge in the pertinent art, the differences between the present invention and the totality of knowledge in this art provided by the reference of record, and the views of the ordinary skilled practitioner do not and cannot provide any expectations or predictive value whatsoever for the methodology. To the contrary, the subject matter of the amended independent claims are unique and unforeseen in this field.

Also, the Examiner has unfortunately failed to appreciate and to fulfill the obligation to evaluate applicants' subject matter as a whole

rather than merely identify the individual characteristic components of the invention as defined by the pending claims. The major differences existing between applicants' defined invention and the totality of knowledge provided by the cited and applied publication of record cannot be ignored because some similarities and points of information are shared in common among them. Under Section 103(a), the Examiner cannot dissect a claim, excise the prior art portion from it, and then declare the remaining portion of the mutilated claim to be unpatentable. Rather the entirety of the claim must be read as a whole [In re Gulick, 217 U.S.P.Q. 401 (Fed. Cir. 1983)].

In addition, the Examiner has failed to prospectively evaluate the claims defining applicants' invention and unfortunately employed selective hindsight unfairly to reject the present invention. It is legally impermissible for the Examiner first to ascertain what applicant's invention comprises factually, and then view the printed publications of record in such a manner as to select from the random facts of those printed publications only those items which could selectively be extracted or modified to reconstruct applicant's subject matter. The Examiner cannot properly employ such a hindsight and selective reconstruction approach to pick and choose among diverse and varying publications in order to depreciate the present invention; rather to conclude that a person of

ordinary skill in this art had knowledge of the presently claimed methodology and compositions when no publication of record can convey or suggest such knowledge in any detail, is to fall victim to selective hindsight evaluation wherein only that which applicants have taught the Examiner is used against its teacher [In re Fine, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); In re Kotzab, 55 U.S.P.Q.2d 313 (Fed. Cir. 2000)].

For all the reasons stated herein, applicants respectfully submit that multiple errors of fact and law have been made by the Examiner; and that, accordingly, independent claims 1-2, 11 and 15 are therefore allowable as presently defined.

Claims 3-10 and 12-14 depend from independent claims 1-2, 11 or 15; and merely provide particular limitations and preferred embodiments to the unique and non-obvious invention defined therein. Since independent claims 1-2, 11, and 15 are believed to be in condition for allowance and claims 3-10 and 12-14 respectively depend there from, these dependent claims are also believed to be allowable.

In view of the above discussion and detailed analysis of the many factual and legal errors presented by the Examiner, applicants believe that this case is now in condition for allowance and reconsideration is respectfully requested. The Examiner is invited to call applicants'

undersigned attorney should she feel that such a telephone call would further the prosecution of the present application.

Respectfully submitted,

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